

**Remarks**

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider and withdraw the outstanding rejections. All amendments have been made without prejudice or disclaimer. Applicants reserve the right to prosecute any unclaimed subject matter in this or another application as desired. Consideration and entry of these amendments and remarks is respectfully requested.

**Claim Status**

Claims 2-3, 5-6, 8-9, 22-23, and 43-45 are currently pending in the application, with claim 45 being the independent claim. Claims 1, 4, 7, and 24-42 were previously cancelled. Claims 10-18 remain withdrawn from consideration as being drawn to non-elected species. No claims are currently amended.

Claim 45 has been amended to clarify the claimed subject matter. As explained below, Applicants do not believe the presently claimed subject matter is in any way disclosed or suggested by the cited art. The claims relate to a two-step method for amplifying one or more polynucleotides of interest by first performing a multiplex amplification reaction followed by, for example, a second amplification reaction such as real-time PCR. As the present claims recite, the first multiplex amplification step is performed in the presence of multiple pairs of primers and oligonucleotide probes that are complementary to the nucleic acids amplified thereby, dividing the products of the first reaction into aliquots, and performing a second amplification step (e.g., real-time PCR) in the presence of at least one of the primer pairs and one of the labeled

oligonucleotide probes used in the first amplification step. It was surprising that the amplification reactions of the claimed methods (especially in the multiplex amplification reactions) could be effectively carried out in the presence a plurality of primers and probes without any detrimental effects (e.g., primer dimerization formation) as described at, for example, Applicants' paragraphs [0012]-[0015], [0082], and [0110]-[0111]. As explained below, the cited art does not describe Applicants' claimed methods.

**Rejections Under 35 U.S.C. § 103(a)**

**A. Rejection of claims 5, 6, 8, 9, 22, 23, 44 and 45**

Claims 5, 6, 8, 9, 22, 23, 44 and 45 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Wittwer et al. (U.S. Pat. No. 6,472,156; "Wittwer") in view of Willey et al. (U.S. Pat. Pub. No. 2003/0186246; "Willey"). Applicants respectfully traverse this rejection for at least the reasons discussed below.

At page 6, the Office Action alleges it would have been obvious to "use the method of diluting first round amplification products as taught by Willey in the real-time methods of Wittwer to perform a second amplification" (emphasis added). However, the Office Action does not provide any evidence that either Willey or Wittwer (taken either alone or in combination) provide any "teaching, suggestion, or motivation" to include a plurality of probes in a first round multiplex amplification reaction (such as that employed by Willey in the absence of any probes) prior to performing a second round of amplification involving real-time PCR (such as that employed by Wittwer). MPEP 2143.01 ("Obviousness can \* be established by combining or

modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so” In re Kahn, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006)”). The Office Action similarly fails to describe any “design incentives and other market forces” that would have provided such motivation. MPEP 2141. Without Applicants’ disclosure in hand, it would have made little sense for the skilled artisan to take a highly complicated multiplex amplification reaction and further complicate it by adding oligonucleotide probes, as is presently claimed. As previously argued, “[p]erforming such a combination would have been believed to simply produce a lot of unwanted non-specific side products, and, at the time, would have been considered a wasteful use of expensive-to-manufacture oligonucleotide probes” (Applicants remarks, Aug. 9, 2009). As pointed out by the U.S. Supreme Court, “[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning.” KSR Int’l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007), citing Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 36 (1966), (warning against a “temptation to read into the prior art the teachings of the invention in issue” and instructing courts to “guard against slipping into use of hindsight” (quoting Monroe Auto Equip. Co. v. Heckethorn Mfg. & Supply Co., 332 F.2d 406, 412 (CA6 1964))). Applicants respectfully maintain that their surprising success with the claimed methods cannot be drawn from the cited references in the absence of hindsight.

The combination of the Wittwer and Willey references simply does not disclose or in any way suggest Applicants’ claimed methods. Neither reference disclose or in any way suggest the inclusion of oligonucleotide probes in a first round multiplex amplification reaction prior to

performing a second round of amplification (e.g., real-time PCR). And the Office Action has not shown that the skilled artisan would have been motivated to do so by those references or, for example, by “design incentives and other market forces” (MPEP 2141). Thus, Applicants do not believe these references may be combined to support a *prima facie* case of obviousness against the amended claims. Withdrawal of the pending rejections is therefore respectfully requested.

**B. Rejection of claim 3**

Claim 3 stands rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Wittwer et al. (U.S. Pat. No. 6,472,156; “Wittwer”) in view of Willey et al. (U.S. Pat. Pub. No. 2003/0186246; “Willey”), and further in view of Park et al. (U.S. Pat. Pub. No. 2004/0146897). Applicants respectfully traverse this rejection for at least the reasons discussed above.

For the reasons stated above, Applicants do not believe that the combination of Wittwer and Willey renders any of the pending claims (including claim 3) obvious. Park is cited as providing “additional types of samples that would be compatible with the multiplex systems of Wittwer and Willey.” However, Applicants do not believe Park cures any of the above-described deficiencies of the combination of Wittwer and Wiley with respect to currently pending claim 3, which is dependent upon claim 45. Thus, Applicants do not believe that the combination of Wittwer, Willey, and Park may be used to support a *prima facie* case of obviousness against currently pending claim 3. Withdrawal of this rejection is therefore respectfully requested.

**C. Rejection of claim 43**

Claim 43 stands rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Wittwer et al. (U.S. Pat. No. 6,472,156; “Wittwer”) in view of Willey et al. (U.S. Pat. Pub. No. 2003/0186246; “Willey”), and further in view of Jansen et al. (U.S. Pat. Pub. No. 2005/0175987). Applicants respectfully traverse this rejection for at least the reasons discussed above.

For the reasons stated above, Applicants do not believe that the combination of Wittwer and Willey renders any of the pending claims (including claim 43) obvious. Jensen is cited as disclosing “a method in which the amplification is carried out in the presence of uracil N-glycosylase.” However, Applicants do not believe Jensen cures any of the above-described deficiencies of the combination of Wittwer and Wiley with respect to currently pending claim 43, which is dependent upon claim 45. Thus, Applicants do not believe that the combination of Wittwer, Willey, and Jansen may be used to support a *prima facie* case of obviousness against currently pending claim 43. Withdrawal of this rejection is therefore respectfully requested.

***Conclusion***

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all presently outstanding rejections. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,  
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